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(54) UTILISATION DE L'ACIDE ASCORBIQUE COMME ACTIF POUR LE TRAITEMENT DE LA SEBORRHEE DANS UNE COMPOSITION COSMETIQUE ET/OU DERMATOLOGIQUE

VERWENDUNG VON ASCORBINSÄURE ALS WIRKSTOFF ZUR BEHANDLUNG VON SEBORRHOE IN EINER KOSMETISCHEN UND/ODER DERMATOLOGISCHEN ZUSAMMENSETZUNG

USE OF ASCORBIC ACID AS THE ACTIVE AGENT FOR THE TREATMENT OF SEBORRHEA IN A COSMETIC AND/OR DERMATALOGICAL COMPOSITION

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(73) Proprietor: **L'OREAL**
75008 Paris (FR)

(72) Inventors:

- **Fanchon, Chantal**
  75015 Paris (FR)
- **Gagnebien, Didier**
  92320 Chatillon (FR)
- **Cantin Hervé**
  91420 Morangis (FR)

(74) Representative:
Lhoste, Catherine
L'OREAL-DPI
6 Rue Bertrand Sincholle
92585 Clichy Cédex (FR)

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Description

[0001] The present invention relates to the use of ascorbic acid as the active agent for the treatment of seborrhea.

[0002] Seborrhea or seborrheic dermatitis is the source for skin inflammation such as flaking on oily faces and scalps, cosmetic disorders which can become the source of dermatosis, such as acne and seborrheic dermatitis.

[0003] Acne is one of the skin diseases mostly affecting age levels between 15 year old teenagers and 30 year old adults. Acne is essentially the result of two intricate phenomena : sebaceous hypersecretion and changes of the keratinisation process of pilosebaceous follicles (hair follicles and its associated sebaceous glands), which resulting in blockages of the pilosebaceous follicles and in the development of retentional acne lesions or comedones. Comedones, as a result of microbial proliferation, can become inflammatory lesions, papules and pustules. Acne is most common during adolescence, but can also continue into adulthood, including in women, for hormonal reasons.

[0004] Acne resulting from sebaceous hypersecretions and changes of the keratinisation process of pilosebaceous follicles is a different disease than what is called Mallorca acne or *acné aestivalis,* which is induced by sun and by an hypersensitive skin to light, and not caused by sebaceous hypersecretions. The German patent filed under No. DE-A-4328871 discloses a photodermatosis (Mallorca acne or *acné aestivalis)* can be treated by using antiixidant compounds, such as ascorbic acid.

[0005] Seborrheic dermatitis is associated with the overgrowth of yeast from *Pityrosporum* colonny on the substrate constituting sebum thereof.

[0006] With acne such as the one from the seborrheic dermatitis, the sebaceous flux regulation offsets the initial cause, i.e. the excessive presence of sebum, and therefore treats the dermatitis.

[0007] This can be noticed with the isotretinoin, for which its oral administration induces sebaceous follicles drying-out and leads to the disappearance of symptoms.

[0008] However, the use of isotretinoin is not free of severe side effects, and therefore remains used for the treatment of severe incapacitating acne forms. Treatments of seborrhea via topic administration have resulted, up to date, in little proven efficacy, and this lack of efficacy is frequently compensated for by systemic administration treatments, including the use of isotretinoin or anti-anhydrous gels.

[0009] Thus, it is observed that the need for topic active agents remains, which has an impact on sebaceous hypersecretion, and therefore on dermatitis associated thereof.

[0010] This is what is disclosed within this invention.

[0011] The claimant has found that ascorbic acid (or vitamine C) was offering anti-seborrheic properties and thus could be used in a cosmetic and/or dermatologic composition as an active agent to prevent skin or scalp seborrhea formation, and against dermatitis resulting thereof, such as acne and seborrheic dermatitis.

[0012] Ascorbic acid antioxidant properties are widely described in the prior art. To illustrate this, the following patents applications EP-A-0 667 145, DE-A-43 28 871, CN-A-1 080 181, FR-A-2 477 871, DE-A-3 514 724, EP-A-0 202 621, EP-A-0 280 606 can be referred to.

[0013] It is known that ascorbic acid is already used in topic compositions as it presents a beneficial effect on skin. And especially, it stimulates the connective tissue synthesis, including collagen, reinforces the cutaneous tissue defenses against damaging effects to the skin, such as ultraviolet radiations and pollution, compensates the deficiency of Vitamin E from the skin, depigments the skin (JP-A-02049714) and presents an anti-free radical property. Ascorbic acid is described as a complexing agent such as ethylene diamine tetra acetate (EDTA) (DE-A-4 305 460). Ascorbic acid is at last described as a promoter of active agent activity contained in cosmetic or pharmaceutic compositions (EP-A-0 599 819).

[0014] Its use for the treatment of seborrhea has never been determined though.

[0015] The present invention thus aims to disclose the use of ascorbic acid in free, esterified or etherified form in and/or for the manufacture of a cosmetic and/or dermatological composition as an active agent for treating seborrhea of the skin and/or scalp.

[0016] The present invention also aims to disclose a cosmetic and/or dermatological treatment process of seborrhea, consisting of applying to the skin and/or scalp a composition containing ascorbic acid as sole agent for treating seborrhea, and more specifically a composition as described herein.

[0017] The composition containing ascorbic acid has a pH ranging from 2 to 5, and more specifically a pH of approximately 4. Ascorbic acid can be used as is or in a stabilized form, for example in a derivative or powder form.

[0018] According to one embodiment of the invention, the composition is in the form of a separate support and solid, which are intended to be mixed together at the time of usage, the solid consisting essentially of pulverulent ascorbic acid.

Such an arrangement is disclosed for example in the patent filed by the claimant under the reference number FR-94-03982.

[0019] The derivatives used for example are the ones obtained by the blockage of the hydroxylic site, especially via esterification or etherification processes with, for example, phosphate, sulfate or alkyl compounds. It then may be related to the Magnesium Ascorbyl Phosphate (MAP), glycosylated form of Vitamine C, ascorbyl acetate and ascorbyl palmitate.

[0020] Ascorbic acid is used, according to the present invention, in an amount preferably ranging from 1 to 20 wt.% and most preferably from 3 to 10 wt.% compared to the total weight of the composition.

[0021] The compositions, according to the invention, can be in any appropriate form for topical application, including in the form of an aqueous, aqueous-alcoholic or oily solution, of a lotion or serum type emulsions, of an aqueous gel, of an anhydrous or oily gel, of a liquid or semi-liquid consistency emulsion such as milk, obtained by a water-in-oil emulsion (W/O) or inversely by an oil-in-water emulsion (O/W), of a suspension or emulsion of a soft, semi-solid or solid consistency, such as in a cream, or gel, of a microemulsion, or of a microcapsule, of a microparticle, or a ionic and/or non-ionic surfactant type vesicle dispersion. These compositions are prepared according to usual processes well known to those skilled in the art.

[0022] The compositions of the invention can comprise adjuvants traditionally implemented in the fields considered as fat bodies, organic solvents, thickening agents, softening agents, antioxidants, screening agents, stabilizers, antifoaming agents, fragrances, ionic or non-ionic emulsifying agents, fillers, sequestrants, dyestuffs, or any other ingredients traditionally used in cosmetics.

[0023] When the inventive composition is an emulsion, the proportion of the water-in-oil phase can range from 5 to 80 *wt.%*, and preferably from 5 to 50 wt.% compared to the total weight of the composition. Oils, emulsifiers and coemulsifiers used within the composition in the form of an emulsion are selected from those traditionally used in cosmetics or dermatology. The emulsifier and optionally the co-emulsifier are present within the composition in an amount ranging from 0.3 to 30 wt.%, and preferably from 0.5 to 20 wt.% compared to the composition total weight. The emulsion can, however, contain lipid vesicles.

[0024] The oils usable in the invention can include mineral oils (vaseline oil), vegetal oils (liquid portion from shea butter), animal oils, synthetic oils (Purcellin oil, Hydrogenated Polyisobutene), siliconized oils and fluorinated oils (perfluoropolyethers). Fats, such as fatty alcohols, fatty acids, and waxes can also be used.

[0025] The emulsifiers usable in this invention can include, for example, esters

from fatty acids and polyhydric alcohols, such as the sorbitol-fatty esters, such as sorbitan tristearate commercialized under the brand name of Span 65® by the ICI company, or also glycerol-fatty esters, such as the glycerol monostearate, or further the esters available at PEG, such as the PEG-40 stearate commercialized under the brand name of Myrj 52® by the ICI company. The emulsifiers can also be silicone emulsifiers such as cetyl dimethicone copolyol commercialized under the branding name of Abil EM90® by Goldschmidt company.

[0026] Hydrophylic gelling agents can include carbopol polymers (carbomers), acrylic copolymers such as acrylate/alkylacrylate copolymers, glycerol poly(meth)acrylates such as the product commercialized under the branding name of Norgel® by the Guardian company, polyacrylamides, including the mixing of polyacrylamide, C13-14-Isoparaffine and Laureth-7, commercialized under the branding name of Sepigel 305® by the Seppic company, polysaccharides, natural gums and clays, and lipophilic gelling agents can include modified clays as bentones, metal fatty acid salts, hydrophobic silica and polyethylenes.

[0027] Additionally, the compositions of the invention can include hydrophilic or lipophilic active agents, including active agents likely to achieve the ascorbic acid effects in the treatment of seborrhea and dermatitis associated thereof, including acne, can consist of anti-inflammatory agents, such as benzoyl peroxide, antibiotics, antiseptic agents such as octopirox, or keratolytic active agents, such as salicylic acid and its derivatives, alpha hydroxy acids, retinoic acid and its derivatives, retinol and its derivatives.

[0028] Additionally, proteins or protéin hydrolysates, amino acids, polyhydric alcohols (glycerol, propytene glycol), urea, allantoine, carbohydrates and their derivatives, water-soluble vitamins, starch, bacterial or vegetal extracts, including Aloe Vera, moisturizers can be used for example as hydrophilic active agents.

[0029] Tocapherol (vitamin E) and its derivatives, essential fatty acids, ceramides, and essential oils can be used as lipophilic active agents.

[0030] The following examples are given as embodiments of the invention without limiting its scope therein. Percentage values are expressed in weight.

Example 1

[0031]

Oily Phase:	
- Abil EM90® (émulsifier)	3%
- Volatile Silicone	12%
- Purcellin Oil	3%
- Bentone gel	5%
- Liquid portion of shea butter	2%
Aqueous *Phase :*	
- EDTA Sodium Salt (sequestrant)	0.1%
- Ascorbic acid	5%
- Water	qsp 100%

[0032] The emulsion manufacturing process is consisting of preparing the oily phase and introducing it into the aqueous phase under stirring conditions.

[0033] The cream obtained is suitable for the treatment of seborrheic dermatitis by using 1-2 daily applications on the face.

Example 2 : Gel

[0034]

- Glycerol Polyacrylate (Norgel®)	29.5 %
- Polyacrylamide/Cl3-14 Isoparaffine/laureth-7 (Sepigel 305®)	2%
- Silicone Oil	10%
- Ascorbic acid	5%
- EDTA Sodium Salt (sequestrant)	0.1%
- Preserving agent	0.4%
-Water	qsp 100%

[0035] The gel manufacturing process consists of mixing the glycerol polyacrylate, Sepigel 305®, sequestrant and ascorbic acid with an aqueous solution, then introducing the silicone oil under stirring conditions.

[0036] The gel obtained is suitable for the treatment of greasy skins by using 1-2 daily

applications on the face.

Example 3 : Cream in the form of a water-in-oil emulsion (W/O)

[0037]

Oily Phase :	
-Span65® - Glycerol Monostearate - Hydrogenated Polyisobutene - Volatile Silicone Oil - PEG-40 stearate (Myrj 52®)	0.9% 3% 6% 7% 2%
Aqueous *Phase :*	
- Polyacrylamide/C13-14 Isoparaffine/laureth-7 (Sepigel 305®) - EDTA Sodium Salt (sequestrant) - Preserving agent -Glycerol - Ascorbic acid - Water	0.9% 0.05% 0.5% 3% 8% qsp 100%

[0038] The emulsion manufacturing process consists of using an homogenizer to disperse the oily phase into the aqueous phase under stirring conditions.

[0039] The cream obtained is suitable for the treatment of acne by using 1-2 daily applications on the face.

[0040] The test below highlights the anti-seborrheic effects of ascorbic acid. The gel used for this test had the following composition (pH=4) :

- Ascorbic Acid	5%
- EDTA Sodium Salt (sequestrant)	0.1%
- Glycol extract from Hamamelis virginia leaf	0.47%
- Sodium Hydroxyde	0.83%
- Citric Acid, 1 HaO	1.24%
- Carrageenan (gelling agent)	1.26%
- Guar chloride hydroxypropyl tri-methylammonium (gelling agent)	0.47%
- Acrylic Polymer in water/glycerol solution at 1 % (gelling agent)	28.5 %
- Isoprene glycol	4.75%
-Preserving agent	0.48%
-Water	qsp 100%

[0041] Trial studies were performed on 3 groups consisting each of 20 volunteers of both sexes (60 subjects total), aged from 18 to 25. One group of 20 volunteers have applied the gel product containing ascorbic acid all over their faces, twice a day (morning and evening) for two months and the two other groups have applied in a similar way placebo gels, one of pH 3, the other of neutral pH.

[0042] Sebaceous secretions were ranked at the beginning of the experimentation (T0), then after 6 weeks of treatment (T6) and after 8 weeks of treatment (T8) using Sebutape® patch, and by subjective evaluation. As some volunteers dropped the treatment, testing was performed on 18 subjects for the gel containing ascorbic acid, and on 19 subjects for the gel of neutral pH.

[0043] Sebutapes® are adhesive patches for collecting the sebum production and allowing to monitor and quantify *in vivo* the sebaceous glang activity and their secretions. They are constituted of a porous polymeric film, covered with an adhesive film which permits very close contact between the skin and the patch. At the mouth of each sebaceous follicle, the secretions of lipids will go through the adhesive film and fill the polymeric film micropores. Thus, they will trigger the apparition of translucide spots in contrast with the white film. The sebaceous glang activity is determined by evaluating the spot count which corresponds to the amount of sebaceous glands, according to a rank ranging from 0 to 4, 0 being the rank when the sopt count is almost nil, and 4 being the rank when the number of spots is very important. This technique permits the evaluation of the seborrheic action of a product.

[0044] Trial studies using Sebutape® patch are performed according the following protocol: the forehead is first cleaned with a 70% alcohol solution, then the skin is swabbed and dried before finally applying the patch Sebutape®. The patch Sebutape® is left for 20 minutes before its removal from which the rank is determined.

[0045] The table below reflects the number of subjects for each rank between 0 and 4 :

	Ascorbic acid-based gel			Gel of pH 3			Gel of neutral pH		
Ranks	T0	T6	T8	T0	T6	T8	T0	T6	T8
0			1						
1		9	9		6	5		8	7
2	11	6	5	10	9	12	14	8	11
3	6	3	3	10	4	3	5	3	1
4	1								

[0046] The analysis of the variance by ranks (Friedman test) indicated a significant diminution of the sebaceous production after the first 6 weeks of treatment compared to T0 for the ascorbic acid-based gel and for the gel with a pH of 3, the results being significantly better for the Vitamin C-based gel (Rank from 0 to 1 for 10 subjects after using the ascorbic acid-based gel on only 5 subjects who used the gel with a pH of 3).

[0047] Additionally, the trial study volunteers made a subjective evaluation of their skin after applying the gel, on a 9-point scale ranging from "very high production of sebum" to "very low production of sebum". The table below reports a medium rank obtained for volunteers from each group and from the difference between the rank at TO and ranks at T6 or T8:

Gel	TO	T6	TO - T6 (%)	T8	T0-T8(%)
Ascorbic acid-based gel	6.3	4.6	-27%	3.9	-38%
Gel of pH 3	5.7	5.1	10.5%	4	-30%
Gel of neutral pH	5.95	5.42	-9%	5.05	-15%

[0048] These results demonstrate that the application of gel containing ascorbic acid results in a significant diminution of sebum hypersecretion after 6 weeks of treatment compared to TO.

Claims

1. Process for the cosmetic treatment of seborrhoea, which consists in applying, to the skin and/or the scalp, a composition containing ascorbic acid as sole agent for treating seborrhoea.

2. Process according to Claim 1, characterized in that the ascorbic acid is in free form.

3. Process according to either one of Claims 1 and 2, characterized in that the composition has a pH ranging from 2 to 5.

4. Process according to any one of the preceding claims, characterized in that the composition has a pH of 4.

5. Process according to any one of the preceding claims, characterized in that the ascorbic acid is used in an amount ranging from 1 to 20 % by weight of the composition.

6. Process according to any one of the preceding claims, characterized in that the ascorbic acid is used in an amount ranging from 3 to 10 % by weight of the composition.

7. Process according to any one of the preceding claims, characterized in that the composition is an aqueous, oily or aqueous-alcoholic solution, a water-in-oil emulsion, an oil-in-water emulsion, a microemulsion, an aqueous gel, an oily gel, an anhydrous gel, a serum or a vesicle dispersion.

8. Process according to any one of the preceding claims, characterized in that the composition comprises at least one lipophilic or hydrophilic adjuvant chosen from preserving agents, antioxidants, chelating agents, fragrances, fillers, screening agents, sequestering agents, essential oils, dyestuffs, hydrophilic or lipophilic active agents, and lipid vesicles.

9. Process according to any one of the preceding claims, characterized in that the composition is in the form of a separate support and solid, which are intended to be mixed together at the time of use, the solid consisting essentially of pulverulent ascorbic acid.

10. Use of ascorbic acid in free form as sole active agent for manufacturing a dermatological composition intended for treating seborrhoea of the skin and/or the scalp.

11. Use according to Claim 10, characterized in that the composition has a pH ranging from 2 to 5.

12. Use according to Claim 11, characterized in that the composition has a pH of 4.

13. Use according to any one of Claims 10-12, characterized in that the ascorbic acid is used in an amount ranging from 1 to 20% by weight of the composition.

14. Use according to any one of Claims 10-13, characterized in that the ascorbic acid is used in an amount ranging from 3 to 10% by weight of the composition.

15. Use according to any one of Claims 10-14, characterized in that the composition is an aqueous, oily or aqueous-alcoholic solution, a water-in-oil emulsion, an oil-in-water emulsion, a microemulsion, an aqueous gel, an oily gel, an anhydrous gel, a serum or a vesicle dispersion.

16. Use according to any one of Claims 10-15, characterized in that the composition comprises at least one lipophilic or hydrophilic adjuvant chosen from preserving agents, antioxidants, chelating agents, fragrances, fillers, screening agents, sequestering agents, essential oils, dyestuffs, hydrophilic or lipophilic active agents, and lipid vesicles.

17. Use according to any one of Claims 10-16, characterized in that the composition is in the form of a separate support and solid, which are intended to be mixed together at the time of use, the solid consisting essentially of pulverulent ascorbic acid.